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EXAMINER

ROBINSON, HOPE A

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| ART UNIT | PAPER NUMBER |
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1653

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/081,864

Applicant(s)

LUKYANOV ET AL.

Examiner

Hope A. Robinson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 15, 16 and 21-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 15, 16 and 21-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status Of The Application

1. Applicant's response to the Office Action mailed September 27, 2004 is acknowledged.

Claim Disposition

2. Claims 10-14 and 17-20 have been canceled. Claims 21-40 have been added. Claims 1-9, 15-16 and 21-40 are pending and are under examination.
3. Applicant's amendments and arguments filed December 22, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn.
4. It is noted that applicant filed a computer readable form of a substitute sequence listing and a paper copy thereof, on January 4, 2005.

Information Disclosure Statement

5. The Information Disclosure Statement filed on October 18, 2004 has been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

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6. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in the prior Office Action.

7. The following grounds of objection/rejection are or remain applicable:

Rejections Maintained:

Specification

8. The specification remains objected to because of the following informalities:

The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as TALONTM, TRIS[®], for example, have been noted in this application (see page 38, line 14 and page 39, line 17 in the amendment to the specification filed on December 22, 2004). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that the specification is amended to delete "Tris-HCl" for example, and insert "TRIS[®] HCL (hydroxymethyl) aminomethane hydrochloride". The examiner has provided examples of trademarks found in the instant specification, not all trademarks are listed above, however, all trademarks need to be addressed.

Correction is required.

Claim Rejections - 35 USC § 112

9. The written description rejection of claims 1-9, and 15-16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item (8) of the Office Action mailed on September 27, 2004 and for the reasons stated below.

Response to Arguments:

Applicants argue that claims are generally allowed, when the art permits, which cover more than the specific embodiment shown (page 17 of the amendment). It is further stated that exemplary methods of producing the mutants claimed and resulting exemplary mutants are provided in the instant specification (page 17). Applicant's state that adequate written description has been provided to support the scope of the claims and conclude that one of skill in the art would have no doubt that the applicant was in possession of the invention as claimed (page 18).

This argument is not persuasive. Firstly, the disclosure in the art can enable applicant's specification, however, does not provide missing written description. Secondly, the issue raised is that the scope of the claims encompass mutants that have not been adequately described, thus applicant was not in possession of the claimed invention. The claims broadly read on mutations that result from substitutions, additions/insertion, frame shifting etc. throughout the entire protein structure with no size limitations and no indication of a conserved region and the instant application only exemplifies basic residues Lys and Arg located near the N-terminus of the protein being

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substituted (i.e. point mutations). Therefore, applicant's statement that the written description provided supports the scope of the claims is incorrect. Furthermore, page 16 of the instant specification indicates that a deletion of stretches such as 10, 20, 50, 75, 100, 150 or more is contemplated. Therefore, the claims encompass a large genus of mutants, which have not been adequately described. The instant specification fails to provide a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties...(see MPEP 2163). Therefore, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptide mutants and cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Therefore the rejection remains.

This response is deemed responsive to the arguments raised on pages 16-18 of the amendment after final.

10. The enablement rejection of claims 1-9, and 15-16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item (9) of the Office Action mailed on September 27, 2004 and for the reasons stated below.

Response to Arguments:

Applicants argue that the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (page 19 of the amendment). Pages 19-27 address

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the Wands factors. Applicant's arguments have been considered, however, are not persuasive, because while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. On page 22 applicants argue that several exemplary applications are provided for the nucleic acids and points to pages 15 and 16 of the instant specification. This argument is not persuasive because the issue raised is the breath of the claims in

view of the disclosure. The claim recites, "In an application that employs a nucleic acid encoding a chromo or fluorescent protein", the claims reads on any or all applications which is not supported by the instant specification. Applicant points to pages 15-16, 24 etc. to provide support for the applications, however, the disclosure indicates that the nucleic acid "can be used or may be used" and lists several applications, however, none is demonstrated. The breath of the claims in view of the disclosure is the issue raised, and the discussions provided do not breathe life into the claims.

At page 23 applicant's state that ample support is provided in the specification on pages 8-9, for example, regarding the claimed mutants, which is the crux of applicant's arguments on pages 27. However, the issue at hand is the make and test position. The examiner has pointed to discussions provided in the instant specification and has considered sections pointed to by applicant, however, mere statements is not sufficient, demonstration by way of empirical evidence or working examples is needed. There is no analogous art; therefore, the instant specification needs to provide adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The claims broadly read on mutants not described, for example, the claims encompass deletion of 150 or more amino acid residues and there is no evidence that the claimed protein structure can tolerate such modifications and retain biological activity. The art provides numerous examples indicating that the protein structure function relationship would be dramatically affected with modifications that are minor in comparison to the ones contemplated in the claimed invention. Applicant is enabled the N-terminal mutation of Lys or Arg, however, is not

enabled for the unspecified amount of mutations that are encompassed in the instant claims. Thus, for all the reasons the rejection remains. This response is deemed sufficient to address the issues raised.

Basis For NonStatutory Double Patenting

11. The provisional obvious-type double patenting rejection of claims 1-3, 5-8 and 16 over claims 1-5, 8-10, 12-15, 16 (a and d), 17, 20 (a, b, d and e), 21, 22-23 and 31 (claim 30 will be renumbered as claim 31) of copending Application No. 10/006,922, is maintained for the reasons of record as set forth in item (11) of the Office Action mailed on September 27, 2004 and for the reasons stated below.

Response to Arguments:

Applicant's arguments state that copending application 10/006,922 is silent as to mutant chromo- or fluorescent proteins that possess a decreased or non-aggregating quality from *Cnidarian* species. It is further stated that while the scope of the claims of the cited reference are directed to a broad genus of nucleic acids that may encompass non-aggregating species, claims directed to the narrower non-aggregating species are patentable within the broader genus. This argument is not persuasive. Claim 1 of the instant application recites, "a nucleic acid present in other than its natural environment that encodes a non-aggregating chromo-or fluorescent mutant of an aggregating *Cnidarian* chromo-or fluorescent protein or mutant thereof". The copending application claim 1 recites, "a nucleic acid present in other than its natural environment, wherein

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said nucleic acid encodes a chromo-or fluorescent protein and is from a non-bioluminescent *Cnidarian* species". Applicant points to a discussion on page 8 of the instant specification. The specification on page 2 discloses that "the non-aggregating feature arises from the modulation of residues in the N-terminus of the protein and the chromo and/or fluorescent feature arises from the interaction of two or more residues of the protein. Further, on page 9 it is disclosed that "...the non-aggregating polypeptides of the present invention have amino acid sequences that differ from their corresponding wild type sequences by a mutation in the N-terminus that modulates the charges appearing on side groups of the N-terminus residues...". The two sets of claims are directed to a non-bioluminescent *Cnidarian* species that is Anthozoan. The copending application recitation of a *Cnidarian* species reads on a *Cnidarian* species that is non-aggregating as the specific species is encompassed in the genus. Therefore, the instant claims obvious over the genus recited in the copending application. Thus, the rejection remains.

12. The provisional obvious-type double patenting rejection of claims 1-3, 5-9 and 15-16 over claims 1-4, 10-14 and 19-20 of copending Application No. 10/845,484, is maintained for the reasons of record as set forth in item (13) of the Office Action mailed on September 27, 2004 and for the reasons stated below.

Response to Arguments:

Applicant's arguments state that while the scope of the claims of the cited reference are directed to a broad genus of nucleic acids that may encompass non-aggregating

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species, claims directed to the narrower non-aggregating species are patentable within the broader genus. This argument is not persuasive. Claim 1 of the instant application recites, "a nucleic acid present in other than its natural environment that encodes a non-aggregating chromo-or fluorescent mutant of an aggregating *Cnidarian* chromo-or fluorescent protein or mutant thereof". The copending application claims are directed to, "a nucleic acid present in other than its natural environment encoding an interconverted mutant of a chromo-or fluorescent protein, wherein said interconverted mutant has opposite fluorescent properties from said chromo-or fluorescent protein". The mutant of the copending application is said to be interconverted, having opposite fluorescent properties which defines the type of mutant, the instant claims is directed to a non-aggregating mutant of an aggregating *Cnidarian* species, thus it has properties opposite that of the parent. The copending application is directed to a mutant having properties that differ from the wild type and the instant claim is directed to mutants having properties that differ from the wild type, both are from *Cnidarian* species that is Anthozoan. Applicant is allowed to be their own lexicographer, however, based on the definition of the terms in the respective specifications, the two sets of claims are obvious variations of each other. A *Cnidarian* encompasses a "aggregating *Cnidarian*" and a mutant of the same species encompasses one has opposite properties to the wild type. Thus, the rejection remains.

New Rejections:

13. Claims 21-25, 27-31 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a nucleic acid present in other than its natural environment that encodes a non-aggregating chromo or fluorescent mutant of an aggregating Cnidarian chromo or fluorescent protein or mutant thereof, wherein said non-aggregating chromo or fluorescent mutant comprises a mutation in at least one N-terminal residue codon, however, the claimed nucleic acid is only defined by a function (encoding a protein) not a structure see for example claims 21-23 and 27-40. In addition, the encoded protein is a mutant of an aggregating *Cnidarian* chromo or fluorescent protein or mutant thereof (see for example claim 21) and the claim does not define a reference point for the mutation as the protein is defined solely by its properties. Claim 21 for example, recites "a mutation in at least one N-terminal residue codon" which means that all residues in the N-terminal can be mutated.

It is noted that on page 2 of the instant specification it is disclosed that the "non-aggregating feature arises from the modulation of residues in the N-terminus of the protein and the chromo or fluorescent feature arises from the interaction of two or more residues of the protein" (see lines 10-12 of page 2). It is further stated on page 9 of the instant specification that "the non-aggregating polypeptides of the present invention

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have amino acid sequences that differ from their corresponding wild type sequences by a mutation in the N-terminus... more specifically basic residues Lys and Arg located near the N-termini of the proteins are substituted (see lines 33-39 of page 9). However, the claims encompass a genus of non-aggregating mutants and aggregating mutants thereof not adequately described in the instant specification. For example, on page 16 of the instant specification it is stated that "the sequence changes may be substitutions, insertions, deletions or a combination thereof. Deletions may further include larger changes, such as deletions of a domain or exon, for example stretches of 10, 20, 50, 75, 100, 150 or more amino acid residues" (see lines 30-33).

Additionally, the source of the non-aggregating mutant might be an aggregating protein already mutated, however, the instant specification does not indicate whether the non-aggregating properties recited in the claims are retained when the encoded protein is subjected to the modifications contemplated. Therefore the parental mutants thereof and the non-aggregating mutants encompass a large genus of mutants. Claims 24 and 25, which recite the specific structure of the protein is directed to fragments of the protein (at least 10 contiguous nucleotides and at least 80% sequence similarity". However, the claims are directed to fragments with no functional limitations to demonstrate retention of function or any biological activity. Moreover, the instant specification does not provide empirical evidence to demonstrate possession of the entire genus encompassed in the claims.

It is noted that on page 38, Table 1 provides wild type and mutated *Anthozoan* proteins (parental aggregating proteins) and Table 2 on pages 39-40 provides mutated

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non-aggregating proteins, which exemplifies point mutations and single deletions.

However, the claims encompass mutations other than point mutations or single deletions which have not been described, therefore, the specification fails to provide a representative number of species for the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. Note that on page 10 of the specification it is disclosed that by N-terminus is meant within about 50 residues from the N-terminus, often within about 25, etc. Further on page 13 at lines 15-17 it is stated that the proteins can contain 25 amino acids, 50 amino acids, 75 amino acids, 100 amino acids or more, which means that an N-terminus having 50 residues can be subjected to mutations wherein Arg or Lys is substituted by any or all neutral or negative residue, which could produce an enormous amount of mutants (see claims 28-31). Moreover, although the specification indicates that basic residues Lys and Arg will be substituted with negatively charged or neutral residues, the instant specification does not describe all possible mutations such as plural substitutions. It is noted that Table 2 provides examples such as R2A, K5E and K9T, however, this is not a representative number of species, as the claims encompasses mutations such a R2 replaced by all the possible neutral and negative residues, or other combinations such as R2A-E-T. Therefore, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptide mutants.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to

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practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In addition, the claims encompass a large genus of nucleic acids, which are not adequately described, see for example claim 34. Additionally, claim 39 is directed to an application that employs the nucleic acid, and the claim encompasses any and all possible applications, which have not been described by the instant specification.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid and the encoded polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993).

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

14. Claims 21-25, 27-31 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid set forth in SEQ ID NOS: 14, 15, 17, 19, 21 and 23, and information provided in Tables 1 and 2 (see pages 38-40 of the specification), does not reasonably provide enablement for any non-aggregating mutant or any aggregating mutant thereof or any nucleic acid fragment or any application employing the nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of parental aggregating mutants and non-aggregating mutants. Additionally, claims are directed to the parental mutants that produce non-aggregating mutants (double mutants). Further, non-aggregating mutants are said to arise from the modulation of residues in the N-terminus (which can span 50 residues) for proteins that can have 50 or 100 or more residues, see pages 2, 10 and 13 of the instant specification. The parental mutants thereof are said to arise from for example, the following wild types: amFP485, cFP484, zFP506, zFP540, drFP585, dsFP484, asFP600, dgFP512 (see page 10), however, there is no indicia as to how much modifications can be tolerated in the wild type structures. The claims encompass mutations that are not exemplified in the tables on pages 38-40. It is noted that the tables reflect for example point mutations, wherein basic residues are replaced, however, the claims also encompass mutations such as Lys or Arg replaced by for example, a tri-peptide or octapeptide consisting of negatively charged or neutral amino acid residues as the instant specification does not limit the amount of residues that can be used to replace the basic residues or enumerate all the positions the replacements can occupy. Moreover, in view of the language of claims 21, 31 and 34, the claimed protein may not be a non-aggregate mutant, a large amount of variability is allowed. In addition, claim 21 for example recites, "...a mutation in at least one N-terminus residue codon", the claim as been interpreted as a change in at least one codon which changes the amino acid residues in the N-terminus. At least one codon change could mean codons TTT (codes for Phe) changed to TTC (codes for Phe); or

codons TTA (codes for Leu) changed to TCT (codes for ser), therefore a large amount of variability exists. A skilled artisan would have to perform undue experimentation to construct the claimed mutant, absent guidance.

The specification on page 9 (see lines 33-35) discloses that the non-aggregating polypeptides of the present invention have amino acid sequences that differ from their corresponding wild type sequences by a mutation in the N-terminus that modulates the charges appearing on side groups of the N-terminus residues, i.e. to reverse or neutralize the charge, in a manner sufficient to produce a non-aggregating mutant of the naturally occurring protein or aggregating mutant thereof (emphasis added). However, the "so called manner sufficient to produce a non-aggregating mutant" is not discussed. It is noted that on pages 8-9 decreased aggregation is discussed, however, the instant specification does not set forth for example, the specific environment such as the solution needed to achieve the properties claimed. The chromo or fluorescent protein once modified to achieve non-aggregation may not function as anticipated as it may not have the same properties of the native/wild-type protein or mutant thereof.

The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified based on the changes contemplated on page 16, for example, or if said protein will be functional or exhibit the same properties or characteristics as the wildtype or parental mutant thereof. In the instant application, the properties of the protein recited in the claims (see for example claim 21) and recitation of a nucleic acid encoding such is insufficient to determine a chemical structure for the mutants encompassed in the claims. Additionally, there is no data

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provided demonstrative of a particular portion of the structure that must be conserved. Further, the claims recite the use of the nucleic acid in an application (see for example claim 39), however, there is no limitation as to what type of application is intended by the claimed invention, which is not supported by the instant specification. Therefore, the claims encompass fragments (claims 21, 24, 25, 34 for example) and mutants that may not have any biological activity or display the desired properties. One skilled in the art would have to engage in undue experimentation to construct an aggregating mutant thereof and then produce from this a chromoprotein or fluorescent mutant that maintains the recited properties. Due to the large quantity of experimentation necessary to generate the infinite number of mutants/fragments recited in the claims and possibly screen same for activity/desired properties and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary

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guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity/properties comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. It is noted that the instant specification provides for example point mutations, however, the claims encompass plural substitutions, which are not exemplified, nor are there examples of all the possible neutral residues in a mutant sequence. Furthermore, the parental sequence can be a mutant of the wildtype subjected to further mutation to form the non-aggregating mutant. The skilled artisan would recognize the high degree of unpredictability that all the fragments/mutants encompassed in the claims would retain the recited properties.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). Therefore, amino acid substitutions are critical to the protein's structure/function relationship. Moreover, the amino acid residues of the claimed invention are substituted to reverse or neutralized the charge appearing on side groups of the N-terminus residues to obtain the non-aggregating mutant, however, the environment that the protein is in, is also critical. It is well known in the art that aggregation can be induced by changes in pH, the salt concentration, valency of ions or the polarity of the solvent, however, the instant specification does not provide any guidance with regard to these factors that can critically affect aggregation, to breathe life into the claims. For example, Lund et al. (Biophysical Journal, vol. 85, no. 5, November 2003, pages 2940-2947) state that solution conditions can prevent or promote aggregation, such as salt concentration, ion valency, pH and or solvent (see page 2940).

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining

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similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity/property, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed mutants as the claims encompass mutants not described in the instant specification. Thus, one of skill in the art would have to engage in undue experimentation to construct the mutants of the claimed invention and examine the same for function/the specific properties.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of mutants/fragments. The claims broadly read on any aggregated mutant thereof or any non-aggregated mutant of said aggregated mutant or any nucleic acid fragment/application. The claims also read on any nucleotide sequence that is "about 80% similar to the given sequences (SEQ ID NO: 14, 15, 17, 19, 21 and 23). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that

"...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Therefore, the instant specification to be enabling need to provide direction/guidance regarding whether the structure of the chromo or fluorescent mutant can tolerate the modifications encompassed by claims and still possess the desired properties or whether a protein that does not have the desired properties may result. Absent sufficient guidance/direction one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and insufficient working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test mutants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible mutants to find one that has the desired properties as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Basis For NonStatutory Double Patenting

15. Claims 21-23, 31, 34-37 and 40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 8-10, 12-15, 16 (a and d), 17, 20 (a, b, d and e), 21, 22-23 and 31 (claim 30 will be renumbered as claim 31) of copending Application No. 10/006,922. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claims 21-23, 31, 34-37 and 40 are directed to a nucleic acid present in other than its natural environment that encodes a non-aggregating chromo- or fluorescent mutant of an aggregating *Cnidarian* chromo- or fluorescent protein or mutant thereof, from a non-bioluminescent *Cnidarian* species that is *Anthozoan*, nucleic acid fragments, a construct comprising a vector, an expression cassette, a cell or progeny and a kit. The copending application claims 1-5, 8-10, 12-15, 16 (a and d), 17, 20 (a, b, d and e), 21, 22-23 and 31 are directed to a nucleic acid present in other than its natural environment that encodes a chromo- or fluorescent

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protein and mutant proteins from a non-bioluminescent *Cnidarian* species which is *Anthozoan* or a non-*Pennatulacean Anthozoan* species, nucleic acid fragments, a construct comprising a vector, an expression cassette, cells or progeny and a kit.

The instant application claims differ because they are directed to a non-aggregating chromo/fluorescent mutant protein. The specification of the instant application indicates that the non-aggregating feature arises from the modulation of residues in the N-terminus of the protein (see page 2 of the instant application).

However, the copending application claims 12 and 14-15 are directed to mutants of the chromo/fluorescent protein encoded by the nucleic acid. Although copending claims 14 and 15 recite point mutations these are encompassed in the broad language of the instant claim 21 "mutant", as mutations can be substitutions, point mutations, frame shift, deletions, etc.

The claims in the copending application recite the language "present in other than its natural environment", which could be interpreted as isolation of the nucleic acid from the cell, or a nucleic acid that is still present in the cell but separated from the whole organism. Further, the copending application claims 3, 5 and 10 are directed to "an isolated nucleic acid", however, such could also be achieved in the present application, as methods of isolating a nucleic acid are routine in the art. Moreover, the instant claimed nucleic acid could be interpreted as naturally occurring or non-naturally occurring, hence the language recited in the copending application is encompassed in the instant claim language.

Although the instant application claims do not recite non-*Pennatulacean Anthozoan* species (see claims 4, 8, 12, 16 and 20 of the copending application) this species is encompassed in the broad recitation of *Anthozoan* recited in the instant claims. Further the instant application claims directed to a fragment of the nucleic acid, a construct, an expression cassette, a cell/progeny and a kit, couldn't be considered patentably distinct over the copending application claims, which are directed to the same subject matter. Although the scope of the claims herein differs, the two sets of claims are directed to similar inventions of a specifically defined species and since the language in the claims is similar. Thus, the instant application claims are an obvious variation of the copending application claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 21-23, 31 and 34-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 10-14 and 19-20 of copending Application No. 10/845,484. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re*

Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claims 21-23, 31 and 34-40 are directed to a nucleic acid present in other than its natural environment that encodes a non-aggregating chromo- or fluorescent mutant of an aggregating *Cnidarian* chromo- or fluorescent protein or mutant thereof, from a non-bioluminescent *Cnidarian* species that is *Anthozoan*, nucleic acid fragments, a construct comprising a vector, an expression cassette, a cell or progeny, a method of making the encoded protein, an application using the subject nucleic acid and a kit. The copending application claims 1-4, 10-14 and 19-20 are directed to a nucleic acid encoding an interconverted mutant of a chromo or fluorescent protein, from a *Cnidarian* species that is non-bioluminescent and is an *Anthozoan* species. In addition, the copending claims are directed to fragments of the nucleic acid, a construct, an expression cassette, a cell or progeny, a method of producing the encoded protein, an application using the nucleic acid and a kit.

The instant application claims differ because they are directed to a non-aggregating chromo/fluorescent mutant protein. The specification of the instant application indicates that the non-aggregating feature arises from the modulation of residues in the N-terminus of the protein (see page 2 of the instant application). However, note that the copending application claims 1-4 are directed to mutants of a chromo/fluorescent protein encoded by the nucleic acid. Although, the claims of the copending application are directed to "an interconverted mutant", the specification of the

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copending application on page 2 disclose that the chromo/fluorescent properties have been interconverted, thus an obvious variation of the present claims.

Further the instant application claims directed to a fragment of the nucleic acid, a construct, an expression cassette, a cell/progeny, a method of producing the protein, an application using the nucleic acid and a kit, couldn't be considered patentably distinct over the copending application claims directed to the same subject matter. Although the scope of the claims herein differs, the two sets of claims are directed to similar inventions of a specifically defined species and since the language in the claims is similar. Thus, the instant application claims are an obvious variation of the copending application claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. No claims are presently allowable.

18. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

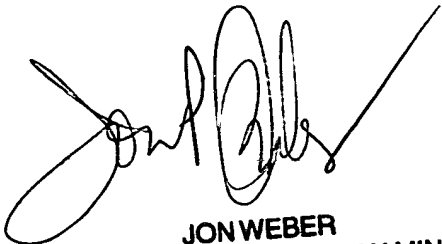
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope A. Robinson, MS ^{HR}
Patent Examiner ^{3/15/05}


JON WEBER
SUPERVISORY PATENT EXAMINER